REMARKS

I. Status of the Claims and Preliminary Remarks

The Applicant would like to thank the Examiner for the personal interview on July 11, 2006, during which proposed claim amendments were discussed. For the Examiner's convenience, attached hereto as Appendix A is a table of the relevant page and line numbers which support the G-CSF modifications discussed in the interview and set out in the amended claims.

Claims 62, 66, 75, 76, 79, and 81-83 are pending in the instant application. Claims 62, 66, 75, 76, and 79 have been amended to more particularly recite the subject matter Applicant regards as the invention. The amendments to the claims do not add new matter.

II. The rejection of claims 62, 66, 75, 76, and 79 under 35 USC §102(b), may be withdrawn.

Claims 62, 66, 75, 76, and 79, were rejected under 35 USC §102(b) as being anticipated by Shaw (US Patent No. 4,904,584). Specifically, the Examiner asserted that Shaw discloses the same lysine substitutions recited in the pending claims. The Examiner asserted that "Shaw teaches that all but 1 to approximately 6 of the original lysines can be deleted and/or replaced." Applicant respectfully traverses.

The specification teaches that helix A ends at about amino acid residue 39 and helix B begins at about amino acid residue 72 (numbering according to figure 1, see p. 25, lines 14-18). Even though the specifications refers to the sequence that connects the A and B helices as the "AB loop" (p. 64, lines 2-5), the entire sequence between helix A and helix B is not a loop region as defined in the specification. Loops are taught at p. 66, lines 31-33 to be "relatively flexible structures compared to the helices" that "tend not to interfere with receptor binding" (p. 18, line 10-11). The sequence connecting the A and B helices, however, includes a secondary structure referred to as the AB helix which is important for receptor binding (See, e.g., page 71 of the specification) along with a four residue 3^{10} helix immediately followed by a six residue alpha helix (see p. 28, lines 19-22) Because of this structure located between the A and B helices, the specification expressly teaches that the AB

loop is located at amino acid residues 58-72 (See, e.g., page 68 of the specification). This region is located at the carboxy terminus of these secondary structures.

Shaw discloses a number of mutated proteins in which lysine residues have been substituted. In Shaw's G-CSF mutant, lysines at positions 16, 23, 34, and 40 (the difference in numbering of amino acid residues resulting from an amino terminal methionine in the G-CSF sequence of the instant application), are substituted with arginine. However as discussed above, none of these residues are located in the AB loop as defined in the instant specification. At best, Shaw discloses sequence modification by substitution of one or more residues in the A helix and a region immediately adjacent the A helix but not in the AB loop. Furthermore, the Examiner's assertion that "Shaw teaches that all but 1 to approximately 6 of the original lysines can be deleted and/or replaced" is inconsequential when one considers that the only lysine residues in the native G-CSF sequence are located at positions 16, 23, 34, and 40 according to Figure 4 of Shaw.

The presently claimed G-CSF mutants are wholly distinct from any mutant described in Shaw. Claims 62 and 66 each recite a G-CSF mutant wherein at least one external loop is modified to include one or more lysine residues not found in the native sequence. Claim 75 recites a G-CSF mutant having the amino acid sequence of at least one of helix C or helix D modified, claim 76 recites a G-CSF mutant having modifications in at least two helices and claim 79 recites a mutant with modifications in at least three helices. None of the above modifications are disclosed or suggested by Shaw which, as discussed above, is limited to the A helix with respect to modification of any amino acid sequence in a helix.

Because the disclosure of Shaw fails to describe each and every limitation in the claims rejected by the examiner, Shaw cannot anticipate the subject matter of claims and the rejection under 35 USC §102(b) must be withdrawn.

V. The rejection of claims 62, 66, 75, 76, 79, and 81-83 under 35 USC §112, second paragraph, may be withdrawn.

Claims 62, 66, 75, 76, 79, and 81-83 were rejected under 35 USC §112, second paragraph, for assertedly being indefinite for failing to particularly point out and claim the subject matter which the Applicant regards as the invention. Specifically, the

Examiner asserted that claims 62 and 66 are indefinite because of the recitation of the phrase "at least one amino acid sequence..." In response, Applicants point out that the phrase "at least one amino acid sequence..." accurately reflects what the Applicant regards as the invention insofar as this phrase encompasses G-CSF loop regions as defined in the specification as filed. In other words, a specified external loop sequence is modified, for example by deletion, substitution, and/or insertion of one or more amino acid residues. If, as the examiner suggested, the claim recited "at least one amino acid residue in an external loop is altered," the claim would not embrace the intended scope. While "altering" a specific amino acid residue can allow for deletion or substitution of that residue, "altering" does not allow for insertion of one or more amino acid residues in the sequence. Accordingly, the Applicant submits that the language to which the examiner object is in fact a clear statement of the invention.

The Examiner further asserted that claims 62 and 75, 76 and 79 are indefinite, in essence for being unclear as to the location of amino acid residues in the various helices which are changed. At the outset, Applicant notes that the Examiner likely meant to indicate claim 66 rather than claim 62 in this instance since claim 62 subparts (a) and b) are silent with respect to any modification in any helix. Accordingly and in response, Applicant points out that claims 66, 75, 76, and 79 have been amended to more particularly recite the subject matter Applicant regards as the invention. Specifically, Applicant submits that the claims as amended clearly recites the minimum number of claimed substitutions and the locations of those substitutions. For example, in claim 66, at least one amino acid residue in a helix is altered (with the noted exception), and this residue can be in the A, C or D helix. Likewise, in claim 75, at least one helix amino acid residue is altered, and this residue is located in either the C or D helix. In claim 76, at least two helix amino acid residues are altered, these two residues are located in separate helices, and they are separately located in helix A, C or D. Finally, claim 79 requires at least three helix amino acid residues be altered, one each in helix A, C and D. The Applicant notes that these helix alterations are described as being only a minimum number of changes.

Accordingly, the amendment to the claims more clearly defines the subject matter of the invention and the rejection of claims 62, 66, 75, 76, 79, and 81-83 under 35 USC §112, second paragraph, may be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

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Respectfully submitted,

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Appendix A

SUBJECT	SUPPORT
Significance of resolving the 3D structure	Page 7, lines 7-22; Page 15, line 12 to page 17, line 32.
G-CSF analogs, in general	Page 8, line 21 to page 9, line 18 Page 15, line 12 to page 17, line 32
Single mutations	Page 47, line 10, through Page 54, line 8
Double mutations	Page 54, line 10, through page 56, line 4
Combinations of mutations	Page 56, lines 5-10 – "any combination of mutagenesis techniques may be used to generate a G-CSF analog nucleic acid having one or more than one alteration."
Modification with PEG	Page 9, lines 26-29 – no specified location Page 11, lines 11-18 – no specified location Page 18, line 7 to page 19, line 5 Page 68, lines 12-21
G-CSF analogs with diminished ability to bind its receptor; G-CSF analogs with diminished ability to stimulate neutrophils	Page 16, lines 6-12
Modification of helices and structural integrity	Page 19, line 24, through page 20, line 7 – helix modifications in general Page 64, lines 9-16 – helix residues required for activity Page 66, lines 9-26 – hydrophobic core residues required for structural integrity Page 71, lines 18-28 – helix residues pointing toward other helices
Use of HPLC to detect structural changes	Page 60, line 29, through page 61, line 5 – peak position from HPLC is an indication of overall similar structure
Modification of external loops	Page 17, lines 3-32 – loop modifications in general Page 18, lines 7-24 – chemical modification of loops, lysine alteration; pegylation Page 67, line 7 to page 68, line 30 – loop modifications to prevent protease

	degradation; altering loop flexibility; stabilizing loops; pegylation
Biological activity of G-CSF analogs	Page 59, line 10 to page 60 line 27 – G-CSF biological assays Table 5 at page 62-63- activity of specific mutants Page 69, lines 19-29 – regions required for receptor binding Page 71, lines 1-14 – regions between the A and B helices required for receptor interaction Page 72, lines 13-16 – two receptor binding domains
Definition of helices and loops	Page 25, lines 14-23 – helix regions defined Page 28, lines 17-22 – overall 3D structure and specific secondary structures; 4 alpha helical bundle; secondary structure between A and B helices, including 3^{10} helix and 6 residue alpha helix Figure 2A Page 68, lines 6-10 – defining AB and CD loop sequences